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### **Authors**

Moghimi, Sasan  
Zandian, Mehdi  
Latifi, Golshan  
et al.

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# Topical Latanoprost Does Not Cause Macular Thickening after Uncomplicated Cataract Surgery

Sasan Moghimi<sup>1</sup>, MD; Mehdi Zandian<sup>1</sup>, MD; Golshan Latifi<sup>1</sup>, MD; Heydar Amini<sup>1</sup>, MD  
Yadollah Eslami<sup>1</sup>, MD; Reza Zarei<sup>1</sup>, MD; Ghasem Fakhraie<sup>1</sup>, MD; Kouros Nouri-Mahdavi<sup>2</sup>, MD

<sup>1</sup>Farabi Eye Research Center, Department of Ophthalmology, Tehran University of Medical Sciences, Tehran, Iran

<sup>2</sup>Jules Stein Eye Institute, University of California Los Angeles, Los Angeles, USA

**Purpose:** To explore changes in central macular thickness (CMT) after a two-month period of glaucoma therapy with topical latanoprost after uneventful phacoemulsification.

**Methods:** Forty-one eyes of 31 patients with primary open angle or pseudoexfoliative glaucoma who required glaucoma medications after cataract surgery were prospectively enrolled. All eyes had undergone uneventful phacoemulsification with intraocular lens implantation at least 4 months before initiation of latanoprost. After a complete ophthalmic examination, spectral-domain optical coherence tomography (SD-OCT) and fluorescein angiography (FA) were performed at baseline before starting latanoprost. All eyes received latanoprost for 2 months, and clinical examinations were repeated one and two months afterwards; OCT and FA were repeated after 2 months. Outcome measures were CMT and loss of more than 2 lines of best corrected visual acuity (BCVA).

**Results:** Mean patient age was 71.6±7.8 years. Intraocular pressure decreased from 21.5±3.4 mmHg to 14.4±2.6 mmHg ( $p<0.001$ ) at 2 months. None of the eyes developed reduction of BCVA exceeding 2 lines, or angiographic cystoid macular edema (CME). Likewise no significant change was noted in CMT (249.9±29.8 vs 248.8±30.7µm), average macular thickness (274.5±15.0 vs 273.8±17.0µm), or macular volume (9.6±1.0 vs 9.6±1.1µm<sup>2</sup>) after treatment as compared to baseline ( $P>0.05$  for all comparisons).

**Conclusion:** Topical use of latanoprost later than 4 months after uncomplicated cataract surgery does not seem to predispose to increased macular thickness or CME and may safely be used in this setting.

**Keywords:** Latanoprost; Macular Thickness; Cystoid Macular Edema

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**Correspondence to:** Sasan Moghimi, MD. Associate Professor of Ophthalmology, Farabi Eye Research Center, Tehran University of Medical Sciences, Qazvin Sq., Tehran, Iran; Tel: +98 21 5541 6134, Fax: +98 21 5541 6134; e-mail: sasanimii@yahoo.com

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## INTRODUCTION

Latanoprost ophthalmic solution 0.005% (Xalatan, Pfizer Inc., MY, USA) has become a popular agent for the treatment of elevated intraocular pressure (IOP) and glaucoma since its approval by the U.S. Food and Drug Administration in June 1996. Despite the efficacy of latanoprost in lowering IOP through an increase in uveoscleral

outflow as a prostaglandin analogue, certain ocular side effects have been associated with this drug since early studies. These include increased iris pigmentation, mild anterior segment inflammation, hypertrichosis, increased eyelash pigmentation, iritis, anterior uveitis, choroidal effusion and cystoid macular edema (CME).<sup>1-3</sup>

It was after several reports of an association

between latanoprost use and CME, and also resolution of CME after discontinuation of latanoprost, that concerns arose about the use of latanoprost especially in patients at high risk of CME. Most of these studies however, reported CME after cataract surgery either in high risk eyes (with torn posterior capsule or aphakia) or when there was blood ocular barrier (BOB) disruption, i.e. during the early postoperative period.<sup>4</sup>

Optical coherence tomography (OCT) has been reported to have high sensitivity and specificity for detecting CME as compared to fluorescein angiography (FA).<sup>5</sup> Yet studies evaluating macular thickness with OCT after use of latanoprost are sparse.<sup>6-12</sup>

Postoperative inflammation after cataract surgery has been evaluated by several authors using laser flare meters which have shown that postoperative flare values return to baseline 8-12 weeks after cataract surgery.<sup>13-15</sup>

In this prospective interventional case series, we studied changes in macular thickness and macular volume using spectral-domain OCT (SD-OCT) after topical administration of latanoprost for a two-month period at least 4 months after uneventful phacoemulsification and intraocular lens (IOL) implantation. We initiated latanoprost at least 4 months after surgery, trying to avoid the period of BOB instability following uncomplicated cataract surgery.

## METHODS

This prospective interventional case series included patients with glaucoma at Farabi Eye Hospital from 2007 to 2009. In accordance with the Declaration of Helsinki on human investigations, informed consent was obtained from all patients. Inclusion criteria consisted of uncontrolled primary open angle glaucoma (POAG) or pseudoexfoliative glaucoma (PXG) and uncomplicated cataract surgery with intraocular lens (IOL) implantation within the capsular bag which was performed by a single surgeon (SM) at least 4 months prior to initiating latanoprost. Exclusion criteria were history of any kind of ocular trauma, diabetic

or inflammatory eye disease, laser procedures and intraocular surgery (including filtering surgery). Patients with anterior chamber IOLs and systemic steroid use were also excluded. Furthermore, patients with cell or flare on slit lamp examination, macular thickness >300 µm and clinical or angiographic CME before administration of latanoprost were excluded.

Eventually, 41 eyes of 31 patients fulfilled the study criteria and underwent a complete ophthalmologic examination including determination of best corrected visual acuity (BCVA), slit lamp biomicroscopy, indirect ophthalmoscopy and IOP measurement using a Goldmann applanation tonometer. Corneal thickness was measured during the day using a pachymeter (Sonomed 200P+Micropach, Sonomed Inc., NY, USA). FA was performed using a fluorescein angiography system (Heidelberg instrument, Heidelberg, Germany) and OCT was performed employing Cirrus SD-OCT (Carl Zeiss Meditec Inc., Germany) for all patients, and macular thickness and volume were recorded.

Xalatan was added to the glaucoma regimen or used as the first line of therapy. Patients were instructed to use an Amsler grid for checking macular function and were asked to report any visual changes. After one month, clinical examinations were repeated and patients were reassessed for drug intolerance, adverse reactions and compliance. At the end of the second month, the ophthalmic examination was repeated and FA and OCT imaging were obtained. On OCT, macular edema was defined as cyst formation, in addition to increased foveal and macular thickness. On FA, incomplete or 360-degree perifoveal hyperfluorescence (clover shaped) due to leakage was considered as angiographic CME. Central macular thickness (CMT), macular volume and presence of any cystoid changes were recorded. Latanoprost was discontinued in case of an increase exceeding 15 µm in CMT, a decrease of more than one Snellen line in BCVA, or leakage on FA. These cases would be followed for a longer period and control OCT would be performed over the next months.

Data analysis was performed using the SPSS software (Version 16, Chicago, USA). The

paired *t*-test was used to compare CMT, IOP and macular volume before and after administration of latanoprost. Student *t*-test was employed to compare the variables between POAG and PXF subgroups. Significance level was set at  $P < 0.05$ .

## RESULTS

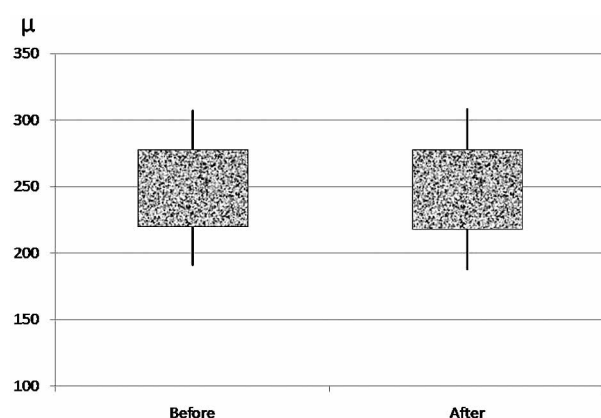
Forty-one eyes of 31 (including 19 male) patients with mean age of  $71.6 \pm 7.8$  (range, 55-87) years were studied. Twenty-eight eyes had POAG and 13 eyes had PXG. Nine eyes were on timolol 0.5% concurrently at the time of study. Mean uncorrected visual acuity was 20/40 (range, 20/50-20/20) before administration of latanoprost.

No significant change was observed in central foveal thickness (Fig. 1), average macular thickness, and macular volume after latanoprost challenge ( $P > 0.05$  for all comparisons, Table 1).

None of the patients experienced a decrease of more than 1 Snellen line in BCVA. There was no case of clinical or angiographic CME after treatment. Mean pachymetry decreased from 539 to 529 microns ( $P < 0.001$ , Table 1) and mean IOP was decreased from  $21.5 \pm 3.4$  to  $14.4 \pm 2.6$  mmHg after using latanoprost ( $P < 0.001$ ).

There were no differences between the POAG and PXG subgroups in terms of changes in IOP, central macular thickness, average macular thickness, macular volume and pachymetry (Table 2).

In one case, central foveal thickness increased by 16  $\mu$ m with no change in BCVA, however



**Figure 1.** Central macular thickness before and after administration of latanoprost.

**Table 1.** Variables before and after latanoprost therapy

	Before	After	P-value
IOP <sup>†</sup> (mmHg)	21.5±3.4 (15-28)	14.4±2.6 (8-19)	0.000*
Central macular thickness (μm)	249.8±29.8 (137-294)	248.8±30.7 (135-295)	0.37*
Average macular thickness (μm)	274.5±15.0 (227-300)	273.8±17.0 (219-312)	0.51*
Macular volume (mm <sup>3</sup> )	9.6±1.0 (5.5-11.0)	9.6±1.1 (5.20-11.3)	0.48*
Pachymetry (μm)	539.8±40.8 (470-623)	529.9±35.5 (470-610)	0.000*

\* Paired *t*-test

<sup>†</sup> Intraocular pressure

**Table 2.** Changes in study variables from baseline in eyes with open angle glaucoma (POAG) and pseudoexfoliation glaucoma (PXG)

	POAG	PXG	P-value
Number	28	13	
IOP <sup>†</sup> (mmHg)	-7.2±3.8	-7.00±2.9	0.85*
Central macular thickness (μm)	0.2±5.9	-3.7±9.9	0.20*
Macular volume (mm <sup>3</sup> )	-0.1±0.3	0.10±0.3	0.07*
Average macular thickness (μm)	0.7±1.1	0.6±1.2	0.84*
Pachymetry (μm)	-10.5±13.3	-8.1±10.8	0.68*

\* Student *t*-test

<sup>†</sup> Intraocular pressure

FA did not show any leakage or abnormality. After discontinuation of latanoprost, the patient was checked for BCVA and SD-OCT, one and three months later which revealed no clinically significant change as compared to baseline.

## DISCUSSION

In the current study, latanoprost was not associated with CME, increased macular thickness or decreased visual acuity in pseudophakic eyes at least 4 months after uncomplicated cataract surgery. CME is a common pathway in many ocular pathologies resulting in cystic accumulation of extracellular intraretinal fluid in the outer plexiform and inner nuclear layers of the retina due to breakdown in the BOB.<sup>8</sup>

Since the introduction of latanoprost, there have been reports of CME in association with its use. Review of the literature implies that latanoprost should be used with caution in eyes with multiple risk factors for CME. Some authors have considered rupture of the

posterior capsule as a relative contraindication for latanoprost use.<sup>7</sup> However, a definite conclusion cannot be made about the causal relation between latanoprost use and CME based on the existing evidence. Eyes afflicted with CME following latanoprost administration in the literature, had many concurrent risk factors for CME.<sup>7,8</sup> Preservatives in many antiglaucoma eye drops have been shown to increase synthesis of prostaglandins and other substances which intensify postoperative inflammation, and the term pseudophakic preservative maculopathy has been proposed for CME caused by eye drops such as timolol and latanoprost.<sup>16</sup> Moreover, pharmacologic studies have demonstrated that latanoprost is not vasoactive even at concentrations well above therapeutic levels.<sup>9</sup> Well-designed controlled clinical trials are needed to elucidate the association between latanoprost and macular changes while excluding other possible causes of CME.

In a study on patients with uncomplicated phacoemulsification cataract surgery, Honyng et al,<sup>10</sup> treated 24 cases unilaterally for 4 weeks and reported no evidence of macular edema (based on FA) or decreased visual acuity. In a retrospective study on 162 pseudophakic eyes after excluding eyes with apparent CME risk factors, 4 cases of CME were detected after uncomplicated cataract surgery associated with latanoprost usage. However, all these 4 cases were taking latanoprost before surgery without discontinuation of the agent. Moreover, CME was diagnosed only based on slit lamp biomicroscopy.<sup>11</sup>

Besides the studies mentioned above,<sup>10,11</sup> there are few case reports describing CME after uncomplicated cataract surgery. In a case report, two pseudophakic eyes receiving latanoprost developed symptomatic CME with blurred vision in the first postoperative month. After discontinuation of latanoprost and initiation of non-steroidal anti-inflammatory eye drops together with oral acetazolamide, their symptoms abated and CME disappeared. The authors recommended use of latanoprost with caution in pseudophakic patients.<sup>12</sup>

To the best of our knowledge, this is the first study addressing administration of latanoprost

in low risk pseudophakic glaucomatous patients utilizing SD-OCT for evaluating the macula. As mentioned above, we excluded patients with high risk characteristics for CME. Postoperatively we followed the patients for at least 4 months, trying to avoid the period of BOB instability due to uncomplicated cataract surgery. In most of the previous studies, CME occurred following uncomplicated surgery while the patients had been using latanoprost perioperatively, i.e. when the BOB is unstable.

We used a newer version of OCT (Cirrus SD-OCT, Carl Zeiss Company) to evaluate central macular thickness, average macular thickness and macular volume. Cirrus SD-OCT is superior to Stratus OCT for evaluating macular thickness.<sup>17</sup>

FA was the gold standard for diagnosis of CME for a long time.<sup>18</sup> Research on novel methods of assessing CME yielded newer findings. Antellif et al<sup>5</sup> reported 96% sensitivity and 100% specificity for OCT (OCT 2000 scanner, Humphrey Instruments, San Leandro, CA, USA) in detecting CME. Moreover, it has been shown that SD-OCT demonstrates greater sensitivity than FA in detecting CME, particularly in cases associated with retinal vein occlusion, diabetic retinopathy and age-related macular degeneration.<sup>19</sup> Another study reported that OCT is as effective as FA in detecting CME but is superior in demonstrating the axial distribution of fluid.<sup>5</sup> It was with respect to these studies that OCT gradually became the standard method for diagnosis of CME.

Macular thickness is a strong and independent predictor of macular edema.<sup>20,21</sup> Nussenblatt et al<sup>22</sup> reported that the degree of macular thickening rather than the presence of macular edema, is significantly correlated with visual acuity. Chan et al<sup>23</sup> demonstrated excellent interobserver, intraobserver and intervisit reproducibility for OCT in detecting macular thickness. Average reproducibility for central foveal thickness was 11  $\mu$ m in healthy patients and approximately 20  $\mu$ m in diabetic patients. Newer OCTs have been reported to have even less variation in measuring central foveal thickness.<sup>24</sup> We considered any change exceeding 15  $\mu$ m in macular thickness as



significant, discontinued latanoprost in such cases and followed the patients more carefully. The same level of change in macular thickness was selected by Sourdille et al<sup>25</sup> for evaluation of CME after cataract surgery. Our sample size with type 1 error of 0.05 had 87% power to detect a 15  $\mu\text{m}$  change in macular thickness assuming a standard deviation of 20 and 35  $\mu\text{m}$  before and after administration of latanoprost, respectively.

In our study, we observed no decrease in BCVA, or change in macular thickness or macular volume; these findings demonstrate that there may be no change in BOB integrity due to latanoprost use following uncomplicated cataract surgery. This is the first time macular volume is used as a criterion for evaluation of BOB. Macular volume may be a useful parameter in assessing BOB, however its sensitivity and specificity need to be determined in future studies.

Postoperative inflammation and the risk of CME might be higher in PXG.<sup>26</sup> We did not detect any difference between POAG and PXG groups in terms of changes in macular thickness or volume, however the number of cases in the PXG subgroup was low in our study.

IOP decreased significantly (mean reduction of 24%) after treatment with latanoprost which is consistent with other reports.<sup>27</sup> We also observed a reduction in central corneal thickness of about 10  $\mu\text{m}$  in POAG and about 8  $\mu\text{m}$  in PXG subgroups in accordance with other studies.<sup>28,29</sup>

Although our sample size was adequate to reveal a significant change in macular thickness detectable by current imaging technology, this study was not powered to detect the potentially small risk of angiographic or clinically significant CME. Another limitation was the fairly short follow-up period. Moreover, our results might not be generalized to other prostaglandins such as travoprost and bimatoprost.

In summary this study did not find any change in macular thickness and volume after administration of latanoprost at least 4 months after uncomplicated cataract surgery; therefore this medication seems to be safe for lowering IOP in these patients.

## Conflicts of Interest

None.

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